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CLINICAL APPROACH TO THE DIAGNOSIS OF DISEASES AND DISORDERS IN PETS AND DOMESTIC ANIMALS SOMETIMES MISTAKEN FOR ANTICOAGULANT TOXICOSIS

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CLINICAL APPROACH TO THE DIAGNOSIS OF DISEASES AND DISORDERS IN PETS AND DOMESTIC ANIMALS SOMETIMES MISTAKEN FOR ANTI-COAGULANT TOXICOSIS

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ABSTRACT: To differentiate the causes of bleeding disorders requires a basic understanding of the hemostatic process and the proper interpretation of history, physical examination, and laboratory tests. A brief overview of the hemostatic process is presented. Tables and flow charts are provided to assist in developing a sound clinical approach to the bleeding patient through the proper assessment of history, physical examination findings, and laboratory tests. Categories of inherited and acquired bleeding disorders are briefly presented.

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INTRODUCTION

Patients with inherited and acquired bleeding disorders are commonly encountered in clinical veterinary medicine. Over the past 40 years, a variety of disease processes that result in bleeding disorders have been described in the veterinary literature. Animals have been found to have most of the inherited and acquired bleeding disorders found in humans (Dodds 1988). Causes of these bleeding disorders can be categorized into abnormalities involving the blood vessel, the platelet, coagulation factors or the fibrinolytic process (Table 1). These abnormalities may occur independently or concurrently and clinical signs associated with them are often very similar. This compartmentalized approach aids in understanding the major processes of hemostasis; however, one must realize that interrelationships exist between all components of the hemostatic process. Clinical and laboratory assessment of the bleeding patient requires a basic understanding of the hemostatic process.

OVERVIEW OF NORMAL HEMOSTASIS

Effective hemostasis is accomplished through a sequence of integrated functions involving the blood vessels, platelets, plasma coagulation factors and the fibrinolytic system (Feldman et al. 1986). When the vessel wall integrity of a small artery or vein is broken, localized vasoconstriction normally occurs. This slows blood flow and facilitates the accumulation of platelets. Also, endothelium damage in a vessel exposes surfaces that promote platelet adherence, platelet aggregation and platelet release reactions. The substances released from platelets further stimulate platelet aggregation, help to maintain vasoconstriction, and contribute to the coagulation process. The initial platelet plug which is formed at the site of injury is stabilized and eventually replaced with fibrin through the complex system of blood coagulation.

Blood coagulation occurs through a series of step-by-step biochemical reactions, in which an inactive coagulation factor is converted to an active coagulation factor. This active factor, in turn, converts another inactive factor to its active form. This cycle continues until fibrinogen is converted to fibrin and the fibrin is cross-linked to form a stable fibrin clot (Figure 1). The coagulation system can be activated and proceed by either of two pathways, the intrinsic system or the extrinsic system. In vivo, activity through both systems is important; however, the concept of two separate pathways helps in the evaluation of laboratory tests and in the categorization of coagulopathies.

The extrinsic system is initiated when tissue extracts (i.e., tissue thromboplastin) are released from damaged endothelial cells and complex with Factor VII. The intrinsic system is initiated when substances such as collagen, platelets or endotoxin activate Factor XII. Both systems share a final common pathway that leads to the formation of a stable fibrin clot. This common pathway begins with the activation of Factor X. Activated Factor X in the presence of calcium and Factor V converts prothrombin (Factor II) to thrombin which in turn converts fibrinogen (Factor I) to fibrin. Fibrin is then cross-linked to form a stable fibrin clot. Eventually, the fibrin clot is removed through the process of fibrinolysis.

CLINICAL ASSESSMENT

Medical History and Physical Examination

The first step in the clinical assessment of the bleeding patient is the development of a complete medical history. The history should contain all of the following: chief complaint, signalment (i.e., age, breed, sex), details of present illness, past medical or surgical problems, health maintenance (i.e., vaccinations, routine diagnostic testing, treatments), previous and

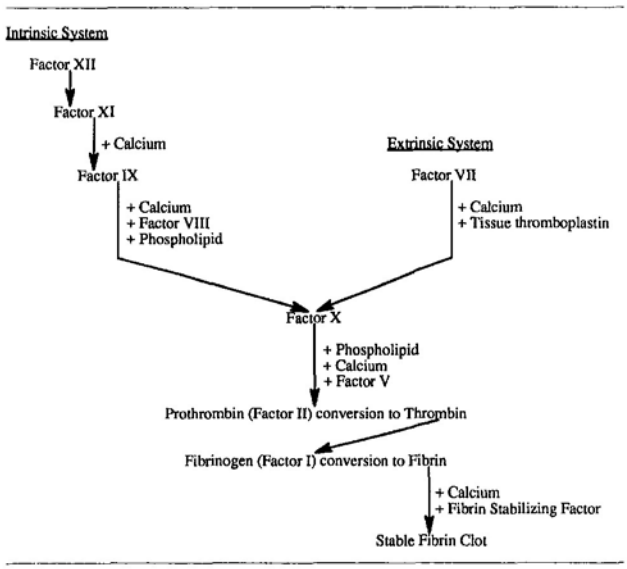

Figure 1. Schematic depicting the intrinsic and extrinsic coagulation pathways.

Table 1. Categorization of hemostatic disorders identified in animals.

- Blood Vessel Disorders
  - Ehlers-Danlos syndrome
  - Hyperadrenocorticism
  - Vitamin C deficiency
  - Diabetes mellitus
  - Immune-complex disease
  - Vasculitis (viral, bacterial and rickettsial causes)
- Platelet Disorders (Thrombocytopenia)
  - Bone marrow production failure
    - Estrogen toxicity
    - Cytotoxic drugs
    - Radiation exposure
    - Myelofibrosis
    - Myeloproliferative disease
    - Immune-mediated destruction of megakaryocytes
    - Infectious diseases (viral, bacterial, rickettsial and fungal)
    - Modified live vaccines
    - Cyclic thrombocytopenia
  - Increased Platelet Usage/Destruction
    - Immune-mediated destruction of circulating platelets (primary or secondary due to neoplasia, drug administration, infectious diseases, blood transfusions)
    - Disseminated intravascular coagulopathy (DIC)
  - Sequestration
    - Splenic torsion
    - Splenic neoplasia
    - Portal hypertension
    - Pulmonary vasodilation
- Platelet Distorders (Thrombocytopathia)
  - Acquired Causes
    - Uremia
    - Non-steroidal anti-inflammatory drugs (e.g., aspirin)
    - Liver disease
    - Myeloproliferative disease
    - Gammopathies
    - DIC
  - Hereditary Causes
    - Thrombasthenia
    - Thrombopathia
    - Von Willebrand's disease
    - Chediak-Higashi syndrome
- Coagulation Factor Disorders
  - Acquired Causes
    - Vitamin K antagonism/deficiency
    - Liver disease
    - DIC
    - Mast cell tumor
    - Heparin therapy
  - Hereditary Causes
    - Factor VIII deficiency (hemophilia A)
    - Von Willebrand's disease
    - Factor IX deficiency (hemophilia B)
    - Factor XII deficiency
    - Factor XI deficiency
    - Factor VII deficiency
    - Factor X deficiency
    - Prothrombin deficiency
    - Hypofibrinogenemia
- Excessive Fibrinolysis
  - DIC

(Modified from Lewis and Dhein, 1990).

present drug history, diet, environment, family history, and a general systems review (e.g., coughing, sneezing, vomiting, diarrhea, discharges, lameness, appetite, water consumption, urination, weight gain or loss, etc.)

Particular attention should be given to the signalment, family history, drug history, and environment (Table 2). The signalment and family history can provide valuable information to support whether the bleeding disorder is inherited or acquired. Inherited disorders tend to become evident early in life, usually during the first 6 to 12 months (Troy 1984). A history of excessive bleeding associated with minor trauma, loss of deciduous teeth, or elective surgical procedures (e.g., ear cropping, tail docking, onchyectomy, ovariohysterectomy, castration, etc.) is supportive of an inherited hemostatic defect. However, some mild forms of inherited hemostatic defects may not be evident until the animal is an adult (i.e., von Willebrand's disease). Information regarding bleeding disorders in close relatives may provide information to support an inherited disorder. Since some inherited bleeding disorders (i.e., hemophilia A and hemophilia B) are transmitted as recessive sex-linked traits, these disorders are seen primarily in the male with the female being an asymptomatic carrier (Johnston 1988). Inherited bleeding disorders are more common in purebred animals and some inherited bleeding disorders occur with a high frequency within a particular breed, for example von Willebrand's disease in doberman pinschers.

A detailed history of recent or current drug administration including vaccinations must be obtained. Drugs such as aspirin and other non-steroidal anti-inflammatory drugs, and some antibiotics interfere with normal platelet function. Modified-live virus vaccines can cause a decrease in platelet numbers for up to 10 days following vaccination (Johnston 1989). Although alone, most of these drugs do not cause clinical bleeding in a normal animal; however, when administered to an animal with a pre-existing hemostatic defect they may lead to a severe bleeding episode. Review of past medical problems and treatments is helpful when attempting to determine underlying or concurrent conditions which could contribute to the hemostatic compromise. Underlying neoplastic diseases, organ failure, infectious agents, and inflammatory processes are likely reasons for hemostatic disorders to occur in the adult animal (Troy 1984). Environmental history is important when attempting to ascertain the likelihood of exposure to toxic drugs or chemicals such as anticoagulant rodenticides.

A complete physical examination must be performed to

Table 2. Historical questions which are essential to ask in the work-up of a bleeding patient.

What is the age, breed and sex of this patient?
Was this bleeding episode spontaneous or was it related to trauma or surgery?
What is the nature of the bleeding (e.g. nosebleed, vomiting blood, hematoma, etc.)?
Have bleeding episodes been observed previously in this patient?
If so, what was the age of the patient when the first bleeding episode was observed?
If so, was the bleeding spontaneous or was it related to trauma or surgery?
If so, what treatment was administered and was the treatment effective?
Has this patient ever received a blood transfusion?
Have immediate relatives ever experienced bleeding episodes?
If so, was the bleeding spontaneous or was it related to trauma or surgery?
If so, were both sexes affected?
What drugs has this patient received in the previous month?
When was this patient last vaccinated?
What type of environment does this patient have access to?
What types of drugs, chemicals or plants are in this environment?
What previous illnesses has this patient had and/or been treated for?

Table 3. Physical findings and their relationship to the hemostatic process.

Physical Finding	Vessel or Platelet Disorder	Coagulation Factor Disorder
Petechiae	Typical	Rare
Ecchymoses	Typical Small, multiple	Typical Large, solitary
Hematomas	Rare	Typical
Hemarthrosis	Rare	Typical
Body Cavity Hemorrhages	Rare	Typical
Superficial Bleeding (seeping type)	Typical	Minimal
Anemia	Typical	Typical

(Modified from Troy, 1984).

determine the nature of the hemorrhage. The nature of the bleeding may be particularly useful when attempting to determine if the bleeding episode is primarily due to vascular, platelet, or coagulation factor abnormalities (Table 3). In an attempt to identify additional diseases or conditions which may be causing or contributing to the hemostatic compromise, physical findings in addition to the bleeding (e.g., fever, lymphadenomegaly, splenomegaly, hepatomegaly, mental status, heart and lung sounds, abdominal distension, joint distension, lameness, icterus, mucous membrane color, etc.) must be noted. These additional physical findings may provide clues as to the cause of the hemorrhage.

Laboratory Evaluation

Although a specific hemostatic abnormality can be suspected from a complete history and physical examination, laboratory testing is usually essential in the determination of a definitive diagnosis. A minimum data base for the patient (e.g., complete blood count, biochemical profile, urinalysis, fecal examination, etc.) should be obtained in an attempt to identify additional diseases or conditions which may be causing or contributing to the hemostatic compromise or which may affect treatment. Laboratory tests for evaluating the hemostatic process can be divided into two categories: screening tests and specialized tests. The screening laboratory tests should be chosen to evaluate all components of the hemostatic process. Once this is accomplished, more specific testing may be required to obtain a definitive diagnosis.

The most commonly performed screening tests (Table 4) include the platelet count, mucosal bleeding time, activated partial thromboplastin time (APTT), activated coagulation time (ACT), one-stage prothrombin time (OSPT), thrombin clotting time (TT), proteins involved in vitamin K absence or antagonism (PIVKA), fibrinogen, and fibrin degradation products (FDPs). Each of these screening tests have been described in detail in previous publications (Davey 1979, Feldman et al. 1986, Johnston 1989, Lewis and Dhein 1990). The clinical applications of the screening tests are depicted in Figures 2 and 3.

Results of the clinical evaluation and coagulation screening tests may dictate that more specific and specialized testing be performed to obtain a definitive diagnosis. Some of the specialized tests include specific factor assays for inherited factor deficiencies, platelet aggregation for platelet function defects, bone marrow evaluation for qualitative platelet disorders, Factor VIII-related antigen for von Willebrand's disease, toxicological assays for anticoagulant rodenticides, and anti-thrombin III levels for the management of DIC.

CLINICAL DISORDERS

Vascular Disorders

Defects in blood vessels may be inherited or acquired. Ehlers-Danlos syndrome is the best described inherited vascular disease in which abnormal collagen weakens vessel support so that bleeding occurs. Acquired vascular disorder may be due to vasculitis. Common causes of vasculitis include immune-mediated mechanisms, viral infections, and rickettsial infections (Troy 1984). Prolonged mucosal bleeding time with the exclusion of thrombocytopenia, platelet dysfunction and normal coagulation tests are the most accessible methods for the diagnosis of vascular abnormalities.

Thrombocytopenia

Thrombocytopenia may be inherited or acquired; however, acquired causes of thrombocytopenia are much more common in veterinary medicine. Thrombocytopenia is due to decreased production, increased usage, increased destruction, or sequestration of the platelets (Table 1). Spontaneous hemorrhage rarely occurs until the platelet count is less than 50,000 per microliter (normal platelet count, greater than 200,000 per microliter). Hemorrhage occurring in patients

Table 4. Screening laboratory tests used to evaluate the hemostatic process.

Laboratory Test	Hemostatic Process Evaluated
Platelet Count	Platelet Disorders (Thrombocytopathia)
Mucosal Bleeding Time	Blood Vessel Disorders Platelet Disorders (Thrombocytopathia)
Activated Partial Thromboplastin Time (APTT)	Intrinsic Coagulation System
Activated Coagulation Time (ACT)	Intrinsic Coagulation System
One State Prothrombin Time (OSPT)	Extrinsic Coagulation System
Thrombin Clotting Time (TT)	Common Pathway in the Coagulation System
Fibrinogen	Fibrin Production
Fibrin Degradation Products (FDPs)	Fibronolysis

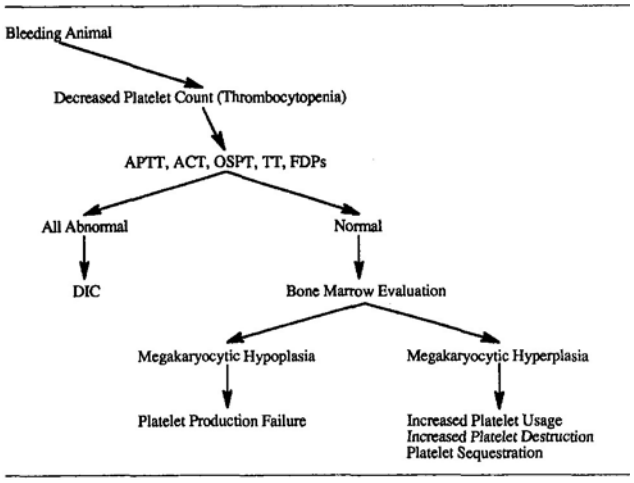

Figure 2. An algorithm for the clinical approach to the patient with abnormal hemostasis and a decreased platelet count (modified from Troy, 1984).

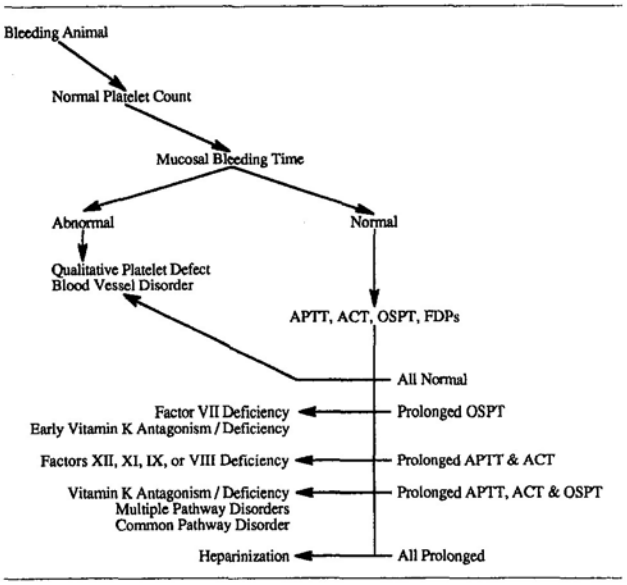

Figure 3. An algorithm for the clinical approach to the patient with abnormal heomstasis and a normal platelet count (modified from Troy, 1984).

with platelet counts greater than 50,000 per microliter is indicative of concurrent vessel abnormalities, platelet function abnormalities, or coagulopathy.

Bone marrow evaluation is indicated in thrombocytopenic animals. Increased numbers of megakaryocytes in the bone marrow is suggestive of diseases causing either increased usage or destruction of the circulating platelet. Whereas, decreased numbers of megakaryocytes in the bone marrow is suggestive of disease processes leading to decreased production.

Thrombocytopathia

Thrombocytopathia or qualitative platelet defects may be inherited or acquired. These defects in platelet function may cause abnormalities in platelet adhesion, aggregation, and release reactions.

Von Willebrand's disease is the most frequently reported inherited thrombocytopathia characterized by decreased platelet adhesiveness. Von Willebrand's disease is inherited as an autosomal recessive or as an autosomal incomplete dominant trait (Troy 1984). In most cases of von Willebrand's disease, spontaneous bleeding is not clinically evident. Bleeding disorders are recognized when an animal undergoes surgery or sustains trauma. However, coexisting disease processes such as hypothyroidism, uremia, liver disease, drug administration, or infections may cause severe bleeding. Von Willebrand's disease has been diagnosed in a large number of dog breeds and occasionally in cats, pigs and horses. A high incidence of von Willebrand's disease has been reported in the following breeds of dogs: doberman pinscher, Shetland sheepdog, golden retriever, German shepherd, Scottish terrier, miniature schnauzer, Welsh Pembroke corgi, Manchester terrier and basset hound. Von Willebrand's disease should be suspected in patients with prolonged mucosal bleeding time with normal platelet counts and coagulation tests. Specific diagnosis is based on Factor VIII-related antigen assay.

Defects in platelet aggregation is seen as an inherited disorder in the otterhound (thrombasthenia) and in the fox hound, basset hound and cats (thrombopathia). Defects of acquired platelet aggregation is most often secondary to drug administration (especially non-steroidal anti-inflammatory drugs) or due to gammopathies.

Table 5. Hereditary coagulopathies and animal species reported to be affected.

Hemostatic Disorder	Species Affected
Factor XII	Feline
Factor XI	Canine, Bovine
Factor X	Canine
Factor IX	Canine, Feline
Factor VIII	Canine, Feline, Equine, Porcine
Factor VII	Canine
Factor II (Prothrombin)	Canine
Factor I (Fibrinogen)	Canine, Equine, Caprine

Hereditary Coagulopathies

Hereditary coagulopathies are less common than acquired coagulopathies. They are generally due to a single factor deficiency. Regardless of the type of coagulopathy, clinical signs are similar. Table 5 provides a listing of reported hereditary coagulopathies and the species affected (Feldman 1986).

Acquired Coagulopathies

Clinically, acquired coagulopathies can generally be viewed as either vitamin K antagonism/deficiency, liver disease, or disseminated intravascular coagulopathy (DIC).

Vitamin K is required for carboxylation of glutamic acid residues in Factors II, VII, IX and X. When these coagulation factors are produced in the absence of vitamin K they are inactive. Since Factor VII (extrinsic system) has the shortest half-life (4 to 6 hours) of the vitamin K-dependent coagulation factors, prolongation of the OSPT is recognized prior to prolongation of the APTT or ACT (Feldman 1981). The PIVKA test detects non-functional precursors of the vitamin K-dependent coagulation factors. The PIVKA test will become positive 12 to 24 hours prior to prolongation of the OSPT (Lewis and Dhein 1990).

Animals require a continuous supply of vitamin K since storage of vitamin K is limited to only a few days. Vitamin K is found in vegetable oils and leafy plants and it is synthesized by gastrointestinal bacteria. Vitamin K is fat soluble and bile acids are required to emulsify fats to facilitate its absorption from the gastrointestinal tract. Vitamin K deficiency may develop due to gastrointestinal disorders (i.e., fat malabsorption, complete bile duct obstruction, pancreatic exocrine insufficiency and gastrointestinal tract sterilization with antibiotics) (Feldman 1981, Feldman 1986). Even though vitamin K deficiency has been reported in animals, vitamin K antagonism secondary to anticoagulant rodenticides ingestion is much more common.

Liver Disease

Bleeding disorders associated with liver disease are often multifactorial. All coagulation factors except for Factor VIII are produced by the liver. Patients with liver disease are often thrombocytopenic. This is partially due to platelet sequestration associated with portal hypertension and splenic enlargement. Patients with liver disease may also develop DIC leading to thrombocytopenia, coagulation factor deficiencies, and increased FDPs. The liver normally aids in the removal of FDPs from circulation. In liver disease, FDPs accumulate and lead to further defects in coagulation. Patients with chronic liver disease may also synthesize an abnormal fibrinogen which interferes with the formation of a stable fibrin clot (Feldman 1981).

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulopathy commonly occurs secondary to a wide variety of clinical conditions. Any disease which produces vascular stasis or breakdown of vascular endothelium favors the induction of DIC. Activation of the coagulation system leads to uncontrolled microvascular thrombosis. Bleeding tendencies develop as coagulation factors and platelets are consumed and these bleeding tendencies are potentiated as FDPs accumulate due to uncontrolled fibrinolysis. Diagnosis of DIC is supported by thrombocytopenia, prolongation of APTT, ACT and OSPT, and elevations of FDPs. Since DIC is always secondary to another disease process, treatment, where possible, must be directed at the underlying cause.

LITERATURE CITED

DAVEY, F.R. 1979. Blood coagulation and its disorders. In: Clinical diagnosis and management by laboratory methods, 16th ed. (J.B. Henry, ed), W.B. Saunders Co., Philadelphia, PA, pp. 1131-1170.

DODDS, W.J. 1988. Introduction to hemostasis. Veterinary Clinics of North America [Small Animal Practice] 18:1-2.

FELDMAN, B.F. 1981. Coagulopathies in small animals. Journal of the American Veterinary Medical Association 179: 559-563.

FELDMAN, B.F., E.J. CARROLL, and N.C. JAIN. 1986. Coagulation and its disorders. In: Schalm's veterinary hematology, 4th ed. (N.C. Jain, ed.), Lea & Febiger, Philadelphia, PA, pp. 388-430.

JOHNSTON, I.B. 1988. Spontaneous or prolonged bleeding. In: Clinical signs and diagnosis in small animal practice (R.B. Ford, ed.), Churchill Livingston, Inc., New York, NY, pp. 103-116.

JOHNSTON, I.B. 1989. Diagnostic approach to the bleeding patient. In: Current veterinary therapy X (R.W. Kirk, ed.), W.B. Saunders Co., Philadelphia, PA, pp. 436442.

LEWIS, D.C. and C.R. DHEIN. 1990. Spontaneous or prolonged bleeding. Kal Kan Forum 9(1): 7-14.

TROY, G.C. 1984. Clinical approach to hemostatic disorders. Veterinary Medicine 79:917-930.